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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,936	08/16/1999	HERMANN OPPERMAN	STK-077	4340

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EXAMINER
ROMEO, DAVID S

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 03/11/2002

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/374,936

Applicant(s)

OPPERMANN ET AL.

Examiner

David S Romeo

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 December 2000.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 5-7 is/are pending in the application.
- 4a) Of the above claim(s) 7 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5 and 6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-3, 5-7 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

The amendment filed 12/27/2001 (Paper No. 15) has been entered. Claims 1-3, 5-7 are pending.

- 5 Applicant's traversal of the restriction is on the ground(s) that the restriction would necessitate the filing of an excessive number of applications, and Applicants maintain their species election and request reinstatement of the restriction requirement mailed 12/14/2000 (Paper No. 8) and reinstatement of claim 7. This is found persuasive in part. Pursuant to Applicants' request, the restriction requirement mailed 12/14/2000 (Paper No. 8) is reinstated.
- 10 This reinstatement is made without prejudice, without waiver, and without disclaimer of issuing a new restriction requirement at any time during the prosecution of this application. Applicants traversal is not persuasive in part because Applicants species election effectively withdraws claim 7 from consideration because it does not encompass the elected species. Furthermore, each of the 1,874,161 embodiments encompassed by the claims are structurally and functionally
- 15 independent and distinct inventions, wherein each can be manufactured independently of the other and used for independent and distinct purposes. It hardly seems fair to, and would prohibitively expensive for, the Office and the examiner to have to examine such numerous inventions in a single application.

- 20 The requirement is still deemed proper and is therefore made FINAL.

Art Unit: 1647

Claims 1-3, 5-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) to the extent that they are drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 9 and 11 and with traverse in Paper No. 15. Claims 1-3, 5-7 are being examined to the extent that they read upon the elected invention.

In the spirit of compromise, the following claim scope is suggested as reasonable:

“A TGF- β superfamily chimeric protein comprising a dimer of two monomers, wherein each monomer comprises the finger 1 domain of OP-1, the finger 2 domain of CDMP-2, and the heel domain of OP-1.”

Any objection and/or rejection of record that is not maintained and/or repeated in this Office action is withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 112

The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5 Claims 1, 2, 5, 6 are indefinite over the recitation of finger 1 subdomain and heel subdomain. Applicants argue that the claims have been amended and request withdrawal of the rejection. Applicants arguments have been fully considered but they are not persuasive. It is unclear if the finger 1 domain and the heel domain are intended or if a subdomain of the finger 1 domain and a subdomain of the heel domain are intended. The metes and bounds are not clearly
10 set forth.

Claim Rejections - 35 USC § 103

Claims 1-3, 5, 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keck (a12) in view of Griffith (v12), Luyten (n12), Qian (u12), Daopin (w12).

15 Applicants argue that the rejection is built upon nothing but hindsight and an obvious to try standard. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the
20 time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Furthermore, Keck gives specific guidance as to the particular

Art Unit: 1647

form of the claimed invention and how to achieve it. Qian provides a reasonable expectation of success and a motivation to select CDMP-2 domains for the chimera because CDMP-2 has chondrogenic activity in vivo but substantially no osteogenic activity and an OP-1/CDMP-2 chimera would provide a practical approach to investigate structure/function relationships of chondrogenic versus osteogenic activity.

Applicants argue that nothing in Keck teaches or suggest the claimed polypeptide. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the present case Daopin teaches a close structural similarity between TGF- β 2 and BMP-2 (page 372, paragraph bridging columns 2-3, last sentence; Table 2), and suggests that the only stable form of TGF- β 2 in solution is a dimer (page 370, column 3, full paragraph 2, last sentence). The interface between the dimers is made largely of hydrophobic residues (page 371, column 1, full paragraph 1). It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a dimer because of the close structural similarity between TGF- β 2 and BMP-2 and the only stable form of TGF- β 2 is a dimer.

Applicants argue that Luyten does not identify the finger 1, heel, and finger 2 regions and that Luyten does not teach or suggest chimeric proteins. Applicants arguments have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413,

Art Unit: 1647

208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the present case at least Keck identifies the finger 1, heel, and finger 2 regions and it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention that the first amino acid residue after the third from the last Cys to the C-terminus of CDMP-2
5 comprises the finger 2 domain of CDMP-2. The first amino acid residue after the third from the last Cys to the C-terminus of the molecule comprise amino acid residues 68 to 98 of SEQ ID NO: 86. Qian teaches that the use of chimeric molecules is a practical approach to investigating the structure/function relationships in closely related proteins (page 6294, left column, full paragraphs 3-4).

10 Applicants argue that Griffith does not teach or suggest the dimeric chimeras. Applicants arguments have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231
15 USPQ 375 (Fed. Cir. 1986). In the present case at least Keck identifies the finger 1, heel, and finger 2 regions and teaches making chimeric monomers that are chimeras of the finger 1, heel, and finger 2 regions. The teaching that there is a close structural similarity between TGF- β 2 and BMP-2 (Daopin at page 372, paragraph bridging columns 2-3, last sentence; Table 2), the suggestion that the only stable form of TGF- β 2 in solution is a dimer (Daopin at page 370,
20 column 3, full paragraph 2, last sentence) and that the interface between the dimers is made largely of hydrophobic residues (Daopin at page 371, column 1, full paragraph 1) and the fact that Qian made a dimer would have motivated one of ordinary skill in the art to make a dimer.

Applicants argue that Qian does not teach the claimed polypeptide. Applicants arguments have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re* 5 *Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the present case at least Keck identifies the finger 1, heel, and finger 2 regions and teaches making chimeric monomers that are chimeras of the finger 1, heel, and finger 2 regions.

Applicants argue that Daopin does not teach or suggest chimeras of TGF-beta 10 superfamily members. Applicants arguments have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re* 15 *Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the present case at least Keck identifies the finger 1, heel, and finger 2 regions and teaches making chimeric monomers that are chimeras of the finger 1, heel, and finger 2 regions.

Applicants argue that there is no teaching or suggestion to combine the references and that there is no motivation to combine the references. Applicants arguments have been fully considered but they are not persuasive. Keck gives specific guidance as to the particular form of 20 the claimed invention and how to achieve it. Qian provides a reasonable expectation of success and a motivation to select CDMP-2 domains for the chimera because CDMP-2 has chondrogenic activity in vivo but substantially no osteogenic activity and an OP-1/CDMP-2 chimera would

provide a practical approach to investigate structure/function relationships of chondrogenic versus osteogenic activity.

Conclusion

5 No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE
10 MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37
CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,
15 however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20 ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.
IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.
25 IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:
 BEFORE FINAL (703) 872-9306
 AFTER FINAL (703) 872-9307
IN ADDITION TO THE OFFICIAL RIGHTFAX NUMBERS ABOVE, THE TC 1600 FAX CENTER HAS THE FOLLOWING OFFICIAL FAX NUMBERS: (703) 305-3592, (703) 308-4242 AND (703) 305-3014.

Application/Control Number: 09/374,936
Art Unit: 1647

Page 9

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.
5 ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

10



DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

15 DSR
MARCH 8, 2002